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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/004,624	11/01/2001	Crystal M. Cunanan	ECV-5630	1582

7590 08/26/2003

Edwards Lifesciences LLC
Law Dept.
One Edwards Way
Irvine, CA 92614

EXAMINER	
WINKLER, ULRIKE	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/004,624	CUNANAN ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *1-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group VIII in Paper No. 8 (claims 50-60) is acknowledged.

The traversal is on the ground(s) that the search for Group I and Group II would not pose a serious burden to search. After reconsideration the restriction between Group I and Group II is withdrawn. Therefore, claims 1-25 and 28 are under consideration in the instant office action.

The traversal of the restriction between group VI and VII is not found persuasive because the agents blocking the binding site are not directed to the same origin and structure.

The requirement is still deemed proper and is therefore made FINAL.

The amendment of paper No.8 does not provide a complete listing of all the claims in the specification, specifically claims 52-60 were not listed. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 50-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims refer to "removing a phospholipid nucleation binding site" the metes and bounds of what is encompassed by "a nucleation binding site" is not clear (specification page 18, lines 20-24). Is the phospholipid the nucleation binding site? Then any method that removes the phospholipid from tissue will be encompassed by these claims or is the "nucleation site" an additional site besides the phospholipid. Clarification of the term is required.

Claims 50-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a method "eliminating or reducing calcification in a biological material", yet do not set out sequential method steps needed to achieve the method. There is an absence or lack of clarity as to the critical method steps and resolution steps or endpoints which reads back on the preamble of the claimed method. Clarification of the method is required.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 50-58 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Lee et al. (U.S. Pat. No. 6,008,292).

The instant invention is drawn to a method of eliminating or reducing calcification in a biological material by removing "removing a phospholipid nucleation binding site" found in the biological material. The biological material is a bioprosthetic tissue. Any method that removes protein or cellular debris from a biological material would fall within the scope of the claim, by removing the undefined "nucleation sites". The method utilizes a surfactant or denaturation agent or both, the surfactant is Tween 80 and the denaturation agent is an alcohol such as ethanol or isopropanol (claims 53-56, 60). The method also requires treating the biological sample with a cross-linking agent, such as an aldehyde (claims 57). Any method that removes protein, lipids and/or cellular debris from a biological material would fall within the scope of the claims by removing "nucleation sites". For purposes of the instant rejections the term "nucleation sites" is interpreted to be phospholipid.

A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process "eliminating or reducing calification in a biological sample" or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Lee et al. discloses a method of preparing collagenous biological material to inhibit calcification by treating the tissue with Denacol and 20% ethanol as well as treating tissue with a mixture of glutaraldehyde, ethanol and Tween-80 (see example 1). The tissue is then treated with polyglycidyl ether either in conjunction or following the glutaraldehyde treatment (see

example 1). Ethanol and Tween are agents known to be capable of solublizing phospholipids. Therefore, the instant invention is anticipated by Lee et al.

Claims 50-58 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Nashef (U.S. Pat. No. 4,729,139).

The instant invention is drawn to a method of eliminating or reducing calcification in a biological material by removing "removing a phospholipid nucleation binding site" found in the biological material. See explanation above.

Nashef discloses utilizing a disinfecting solution for the processing of bioprosthetic tissue comprising formaldehyde, ethanol and tween-80 (see example 1). Ethanol and Tween are agents known to be capable of solubelizing phospholipids. Formaldehyde is a well-known sterilization/ disinfecting agent. Therefore, the instant invention is anticipated by Nashef.

Claims 50-52 and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by Vyavahare et al. (Circulation, 1997).

The instant invention is drawn to a method of eliminating or reducing calcification in a biological material by removing "removing a phospholipid nucleation binding site" found in the biological material. See explanation above.

Vyavahare et al. disclose the removal of phospholipid from a glutaraldehyde fixed bioprosthetic tissue using an ethanol wash (see table 1). Since phospholipids are interpreted to be the calcium nucleation sites the removal of the phospholipid from the tissue results in the

elimination or reduction of calcification. Therefore, the instant invention is anticipated by Vyavahare et al.

Claims 50-58 and 60 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated Cunanan et al. (U.S. Pat. No. 6,214,054) as evidenced by Vyavahare et al. (Circulation, 1997).

The instant invention is drawn to a method of eliminating or reducing calcification in a biological material by removing "removing a phospholipid nucleation binding site" found in the biological material. See explanation above.

Cunanan et al. disclose a method of preparing bioprosthetic tissue (see claims) using a combination formaldehyde, ethanol and Tween (see claim 16) for the processing of the tissue. Vyavahare et al. show that ethanol treatment is effective at removing phospholipids (see table 1). Therefore, the instant invention is anticipated by Cunanan et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 50-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nashef (U.S. Pat. No. 4,729,139) in view of Mirsch et al. (U.S. Pat. No. 6,121,041).

The instant invention is drawn to a method of eliminating or reducing calcification in a biological material by removing "removing a phospholipid nucleation binding site" found in the biological material. See explanation above.

Nashef teaches utilizing a disinfecting solution for the processing of bioprosthetic tissue comprising formaldehyde, ethanol and tween-80 (see example 1). Ethanol and Tween are agents known to be capable of solubelizing phospholipids. Formaldehyde is a well-known sterilization/ disinfecting agent. The processing taught Nashef achieves reduced calcification of the bioprosthetic tissue. The reference does not teach adding a phospolipase.

Mirsch et al. teach a method of decellularizing tissue using microorganisms. Calcification appears to be the primary process leading to degradation of bioprosthetic tissue (column 1, lines 60-61). Non-viable cells present in transplanted tissue are sites for calcium deposition (column 2, lines 7-11). Microorganism are known to produce various enzymes including nucleases, proteases and phospholipases. Lysed cells can provide a source of enzymes and other material effective for decellularization (column 8, lines 5-10). The microorganisms can be removed by soaking, rinsing or filtration. The reference does not teach using a formaldehyde, ethanol and Tween-80 solution to render the tissue suitable as a bioprosthetic.

It would have been obvious to one of ordinary skill in the art to utilize the enzymes produced by microorganism (Mirsch et al.) and combine them with the cleansing process (Nashef). One having ordinary skill in the art would have a high expectation for success in combining the two methods each of which reduces the potential for calcification of the bioprosthetic material. Therefore, the instant invention is obvious over Nashef (U.S. Pat. No. 4,729,139) in view of Mirsch et al. (U.S. Pat. No. 6,121,041).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 50-58 and 60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6,214,054 in view of Vyavahare et al. (Circulation, 1997). Although the conflicting claims are not identical, they are not patentably distinct from each other because the method disclosed in U.S. Patent No. 6,214,054 will result in the removal of phospholipid form the fixed bioprosthetic tissue, as evidenced by Vyavahare et al. in which the phospholipid removal with ethanol treatment of

glutaraldehyde fixed bioprosthetic tissue was evaluated (see Vyavahare et al., Circulation, Table 1).

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 9/25/03